REMARKS

Claims 35, 46, 59, 60, 64-66, and 68-90 are pending with claims 46 and 69-84 currently under examination. Applicants amended claims 46, 70, 72, 74, 76, 78, and 80 to recite a "peptide linker having a cleavage site that is not present in the TARG and TOX peptides." The specification (WO 02/061105) supports this amendment at, for example, the paragraph spanning pages 25 and 26. Applicants also amended claims 77, 79, and 81 to provide an antecedent basis for the peptide linker recited in those claims.

Applicants acknowledge with appreciation the Office's withdrawal of the prior obviousness rejection. Office Action at p. 2. In the Office Action, the Office imposes a new rejection of claims 46 and 69-84 under 35 U.S.C. § 103(a). Applicants address this rejection below.

The Office rejects claims 46 and 69-84 under 35 U.S.C. § 103(a) as allegedly obvious over Aqeilan et al., *FEBS Lett.* 457(2):271-76 (1999) ("Aqeilan") in view of Kim et al., *J. Immunol.* 159(4):1666-68 (1997) ("Kim"), U.S. Patent 6,713,280 ("Huang"), U.S. Patent 6,235,872 ("Bredesen") and Sela and Zisman, *FASEB J.* 11(6):449-56 (1997) ("Sela"). *Id.* at 3. According to the Office, Aqeilan teaches a chimeric protein comprising an apoptosis-inducing protein, the human Bax protein, for targeted therapy. *Id.* Acknowledging that Aqeilan does not teach peptides consisting of SEQ ID NO: 239 or SEQ ID NO: 269, the Office turns to Huang and Bredesen. *Id.* at 3 and 4. Huang allegedly teaches a method of using peptide conjugates for intracellular targeting of Bcl-2, where the peptides include the sequence set forth in SEQ ID NO: 239. *Id.* at 3. Bredesen allegedly teaches linking the peptide sequence set forth in SEQ ID NO: 269 to

a number of proapoptotic peptides because the peptide sequence set forth in SEQ ID NO: 269 does not alter the function of the peptide it is attached to and is allegedly well known for facilitating cellular entry. Office Action at p. 4. The Office reads Kim as teaching the ability of the HIV-1 tat protein to transport macromolecules into cells and identifying a motif that is present in SEQ ID NO: 269, RKKRRQRRR, as necessary for functional translocation. Kim also allegedly teaches using a peptide spacer of a cysteine and three alanines for conjugation of a chimera containing one or more tat peptides and the protein, OVA. *Id.* The Office notes that none of the above references teach the use of D-amino acids and cites Sela for the alleged teaching that inclusion of D-amino acids may be an advantage in terms of specificity and efficacy because of longer persistence. *Id.*

Combining these references, the Office concludes that it would have been obvious to one of ordinary skill in the art to modify the methods taught by the references to make a bifunctional, chimeric molecule comprising D-amino acids that enters the cell and induces apoptosis. *Id.* The Office contends that one would have been motivated to do so because killing cells via apoptosis minimizes tissue damage or systemic response, as allegedly taught in Aqeilan. According to the Office, the skilled artisan would have a reasonable expectation of success given the knowledge that elevations in Bax protein levels are induced in several clinically relevant settings where cell death occurs. *Id.* at 5. In addition, Bredesen allegedly successfully used the peptide set forth in SEQ ID NO. 269 (SEQ ID NO: 52 in the reference) for proapoptotic peptides without altering its function. *Id.* Applicants respectfully traverse.

All of the Applicants' claims relate to chimeric bifunctional molecules having the formula: Targ-Tox, wherein Tox and Targ each *consist* of a peptide as defined by the claims. Thus, each of the claims describe a very specific set of peptides that can be used as the Targ component of the chimera or the Tox component of the chimera. As Applicants explain below, the Office's alleged motivation to combine the cited references is inconsistent with the specificity of the rejected claims. In addition, the claims also describe a peptide linker that covalently links the Targ peptide to the Tox peptide, wherein the linker has a cleavage site that is not present in the Targ and Tox peptides.

The Office contends that the skilled artisan would have been motivated to make the claimed chimeric, bifunctional molecules of the invention because killing cells via apoptosis minimizes tissue damage or systemic response. This alleged motivation to combine does not speak to the specific nature of the invention, which is a chimeric, bifunctional molecule comprising specific peptide sequences. Indeed, the Office's alleged motivation to combine does not explain why the skilled artisan would be motivated to specifically pick the peptide of SEQ ID NO: 239 as the Tox component when Huang teaches this peptide as one of several peptides. Specifically, Huang discloses the peptide sequence of SEQ ID NO: 239 as one of 57 other Bcl-2 blockers. *See* Tables 1, 2, and 3. The only motivation to choose SEQ ID NO: 239 in particular in light of Huang comes from the instant specification. Applicants' own work cannot be used as a foundation for obviousness. None of the other references cited by the Office teach this peptide sequence.

Although Applicants disagree with the Office's alleged ground for a motivation to combine, Applicants have amended claims 46, 70, 72, 74, 76, 78, and 80 to recite a "peptide linker having a cleavage site that is not present in the TARG and TOX peptides." Neither Aqeilan, Huang, Bredesen, nor Sela teach the use of a peptide linker let alone one with the recited cleavage site. The Office contends that Kim teaches a peptide spacer of one cysteine and three alanines and apparently considers this spacer as analogous to the recited peptide linker. Even if this comparison between the spacer and the linker were possible, Kim still fails to teach a linker that has a cleavage site that is not present in the Targ and Tox peptides. As such, because none of the cited references teach this peptide linker, the invention of claims 46 and 69-84 is not obvious. Applicants request that the Office withdraw this rejection.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of claims 46 and 69-84.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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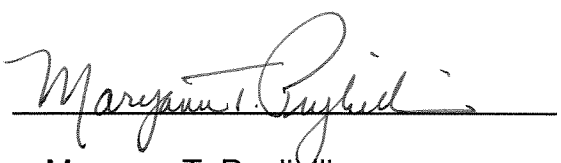
By: 

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